Application Title:	CELL LINE
Inventor:	Charleata A. Carter Ph.D.
Serial No.	09/819,193
Filing Date:	03/28/2001
Attorney Docket No:	8263.003
Examiner:	Karen A. Canella Ph.D.
ART UNIT NO.	1642

III. REMARKS:

a. Regarding Amendments to Claims:

In response to the Examiner's concerns regarding the limitation "having characteristics consistent with primary tumor" in claims 21 and 26, and the limitation "substantially equivalent ways of said specimen" recited in claim 26, said claims have been amended to delete said limitations.

Claim 22 has been amended to distinguish these cells from the AC-258 and KLE cell lines.

b. Regarding 35 U.S.C. §112, ¶2 Rejections:

Claims 21 – 30 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In response to the Examiner's concerns regarding the limitation "having characteristics consistent with primary tumor" in claims 21 and 26, and the limitation "substantially equivalent ways of said specimen" recited in claim 26, said claims have been amended to delete said limitations. Applicant respectfully submits that amended claims 21 and 26 distinctly claim the subject matter which Applicant regards as the invention. Applicant has also cancelled claim 30.

Claim 25 is rejected under 35 U.S.C. §112, second paragraph, as being vague and indefinite in the recitation of a karyotype including "?" because, according to the Office Action, the "?" indicates questionable identification of chromosome or chromosome structure. Applicant respectfully submits that the specification adequately discloses the karyotype of the cell line; patent law does not require that the precise structure of all 48 chromosomes be completely characterized. For example, U.S. Pat.

4,393,133 issued for a cell line having at least one "?" in its karyotype. What is important is that the specific karyotype disclosed in the specification distinguishes these cells from all other prior art. No other known poorly differentiated human endometrial adenocarcinoma cell line exhibits this specific karyotyptic signature of 48 chromosomes including trisomy at chromosomes 3, 7 and 17 while being haploid at chromosome 14. The question marks ("?") represent only a few minor chromosomal deletions and/or cryptic translocations.

Claim 30 is rejected under 35 U.S.C. §112, second paragraph, as being vague and indefinite because, according to the Office Action, the specification lacks a definition that would distinguish "superficially invasive" from "invasive". Applicant has cancelled claim 30.

c. **Regarding 35 U.S.C. §112, ¶1 Rejections:**

Claim 25 is rejected under U.S.C. §112, first paragraph, as failing to comply with the enablement requirement for lacking a deposit of biological material. Applicant respectfully reiterates her intention, noted by the Examiner, that specimens of the invented cells will be deposited in the American Type Culture Collection or other acceptable depository upon notification that such deposit is essential to the patentability of the invention. The Examiner previously graciously agreed to hold this rejection in abeyance. Applicant represents that said deposit will occur promptly upon indication that the same is the final remaining obstacle to patenting.

Claim 30 is rejected under U.S.C. §112, first paragraph, as failing to comply with the written description requirement because, according to the Office Action, the limitation "superficially invasive" is not supported by the specification. Applicant cancelled claim 30.

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d. Regarding 35 U.S.C. §102(b) Rejections:

Claims 26 - 30 are rejected under 35 U.S.C. §102(b) as being anticipated by Carter, et al. (Anticancer Research, 1997, Vol 7, pp. 1973-1984, "Carter 1997") as evidenced from the abstract of Siddiqui et al. (British Journal of Cancer, 1994, Vol. 69, suppl. 21, page 18, "Siddiqui"). As noted above, Applicant has amended claim 26 to remove any uncertainty attributable to the limitations "cells having characteristics consistent with primary tumor" and cells responding "in substantially equivalent ways at the cellular level"; claim 26 was also amended to reinforce that the cells originate in a primary tumor, and that they differentiate in response to anti-cancer compounds. The word "differentiation" means changes in morphology, enzyme activity or protein composition such as, for example, cellular differentiation that may represent a qualitative change in phenotype that is the consequence of changes in gene expression, ultimately leading to a specific functional competence. The specification discloses that KLE cells were obtained from a metastatic endometrial adenocarcinoma *lesion* that metastacized to the *colon* of a patient pretreated with chemotherapy, and that they appear much larger and more irregular than CAC-1 cells; the original paper characterizing KLE cells is Richardson, et al., 1984, Gynecologic Oncology, 17: 213-230, which discloses that KLE cells are from a metastatic lesion of poorly differentiated human endometrial adenocarcinoma cells of the colon.

A different gene expression signature is present in cells from a primary tumor than in cells from metastatic adenocarcinomas. (Ramaswamy, S., et al., 2003. A molecular signature of metastasis in primary solid tumors; Nature Genetics, vol. 33: pp. 40-54.) Modern genomic methods have revealed differences at the cellular and molecular level between cells isolated from primary tumors

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versus cells isolated from metastatic lesions. The extracellular protein environment regulates gene expression. (Kenny, P.A. and Bissell, M.J. 2003, Tumor Reversion: correction of malignant behavior by microenvironmental cues. Intl. J. Cancer. 107: 688-695.) Cells from a primary tumor in the endometrium are thus different from cells that have metastasized to other organs, because each organ and tissue layer contains a different composition of extracellular proteins. A different gene expression signature is present in cells from a primary tumor than in cells from metastatic adenocarcinomas. (Ramaswamy, et al., 2003, Nature Genetics; Vol. 33: 40-54.) Metastatic cells express proteins to digest blood vessel walls, permit travel to distant sites, induce reattachment to a secondary site, and grow as a metastatic lesion. For example, metastatic cells synthesize proteases that can digest blood vessel walls so said cells can cross the blood vessel walls and enter the vascular circulation. KLE cells also grow more slowly than CAC-1 cells. (Application, page 18 lines 6 – 9.) Cells from a metastatic lesion possess a different gene expression signature than cells from a primary tumor, making KLE cells distinctly different from cells from a primary endometrial tumor, such as CAC-1 cells. The minor reorganization of F-actin in the KLE cells is only one aspect of differentiation. Carter 1997 discloses that KLE cells exhibit some reorganization of F-actin in response to retinoic acid treatment, but cytoplasmic mucins remained absent. CAC-1 cells enlarge in response to retinoid acid (Application, Figure 5.) Cell enlargement is another mark of differentiation. KLE cells do not enlarge in response to retinoids. Moreover, CAC-1 cells adhere more tightly to the substrate upon retinoid acid treatment (Application, Figure 6), indicating that they are highly stationary in response to retinoids. Neither this functional change nor cell enlargement in response to retinoids has been demonstrated for KLE cells.

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Due to cellular differences between KLE cells and the cells of claim 26, KLE cells are not as responsive to retinoic acid treatment. Cells originating from a primary tumor of a poorly differentiated endometrial adenocarcinoma are patentably distinct from cells originating from a lesion of the colon.

Applicant notes that, it has not been demonstrated by Siddiqui or Carter 1997 that KLE cells either enlarge or exhibit a reversion to a stationary phenotype upon retinoic acid treatment. Siddiqui only teaches and examines retinoic acid receptors in KLE cells. Moreover, an anticipation rejection may be based on only one reference; and in any event, since Siddiqui predates Carter 1997, Siddiqui does not evidence anticipation by Carter 1997.

Claims 21 – 24 and 26 - 30 are rejected under 35 U.S.C. §102(b) as being anticipated by Gal et al. (Gynecologic Oncology, 1982, Vol. 13, pp. 50-57, "Gal"). As noted above, in response to the Examiner's concerns regarding the limitation "having characteristics consistent with primary tumor" in claims 21 and 26, and the limitation "substantially equivalent ways of said specimen" recited in claim 26, said claims have been amended to delete said limitations. Also as noted above, claim 26 was also amended to reinforce that the cells originate in a primary tumor, and that they differentiate in response to anti-cancer compounds.

The Office Action states that Gal discloses that the tumor from which the cell line was derived was a stage Ib, Grade 3 tumor, which was metastatic. Applicant respectfully submits that the cells disclosed in Gal were from a lesion, not a primary tumor; accordingly, the evidence and contentions set forth hereinabove concerning the KLE cells applies equally here as well.

The Office Action notes that Gal discloses that the average number of chromosomes per cell

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was 64.8; Applicant has amended claim 22 to claim cells that have an average of 48 chromosomes, rather than at least 48 chromosomes.

According to the Office Action, Gal discloses that histological evaluation of tumor explants revealed the same morphological identity as the tumor. Applicant respectfully notes that while histological evaluation may have been state-of-the-art in 1982 when the Gal paper was published, technological advances have allowed a more refined distinctions to be made between cell characteristics. For example, modern genomic methods have revealed several significant differences at the cellular and molecular level between cells isolated from primary tumors versus cells isolated from metastatic lesions. The extracellular protein environment regulates gene expression (Kenny, P.A. and Bissell, M.J. 2003; Tumor Reversion: correction of malignant behavior by microenvironmental cues. Intl. J. Cancer. 107: 688-695.) Cells from a primary tumor in the endometrium are thus different from cells that have metastasized to other organs because each organ and tissue layer contains a different composition of extracellular proteins. A different gene expression signature is present in cells from a primary tumor than in cells from metastatic adenocarcinomas. (Ramaswamy, et al., 2003, Nature Genetics. 33: 40-54.) Moreover, metastatic cells express proteins to digest blood vessel walls, permit travel to distant sites, induce reattachment to a secondary site, and grow as a metastatic lesion. For example, metastatic cells synthesize proteases that can digest blood vessel walls so said cells can cross the blood vessel walls and enter the vascular circulation. Cells originating from a primary tumor of a poorly differentiated endometrial adenocarcinoma are patentably distinct from cells originating from a lesion.

The Office Action states that although Gal does not specifically disclose that the cells were triploid at chromosomes 3 and 17, Gal discloses that trisomy was common. Applicant respectfully submits that Gal discloses (at page 55, lines 6 and 7) that chromosome 17 was not identified; this means that chromosome 17 was missing or moved to areas of other chromosomes. At any rate, it prevents a trisomy of chromosome 17 from being possible in the AC-258 cells described in Gal . The specific individual chromosomes involved in trisomy is critical; for example, Down's syndrome is due to a trisomy of a single chromosome (number 21). (Williams, et al., 1975, Amer J. Human Genetics, 27: 478-485.) Thus, the specific trisomy pattern of the cells of the present invention (i.e., karyotypic signature of 3, 7 and 17 trisomy), is unique in CAC-1 cells and is critical to the characteristics that make this cell line patentably distinct.

The Office Action states that, although Gal does not disclose that the AC-258 cell line includes cells which would respond to an anti-cancer compound in substantially equivalent ways as the specimen from whence they came, Gal does disclose that growth of the tumor *in vitro* appeared to mimic its *in vivo* virulence; according to the Office Action, it would therefore be inherent in Gal that AC-258 cells would respond to an anti-cancer compound in substantially equivalent ways. Applicant respectfully submits Gal is not a proper anticipatory reference for rejecting any claim concerning cellular response to an anti-cancer compound, primarily because Gal does not even purport to deal with such matters. Gal merely characterizes a cell line, without mentioning any cancer characteristics or cellular response to anti-cancer compounds. Applicant respectfully submits that the sentence quoted in the Office Action was misunderstood by the Examiner; that sentence concerning *in vitro*

Applicant respectfully submits that the amendments and contentions set forth hereinabove fully distinguish the present invention from all of the prior art cited in the Office Action.

growth was expressly intended only as a possible factor in cell line establishment, rather than to postulate the cell line's response to anti-cancer compounds.

The Office Action attempts to place the burden upon Applicant to prove that the claimed invention is different from the prior art. However, any such burden does not require Applicant to prove the negative proposition sought by the Office Action, namely, that the cells disclosed in Gal do not respond to an anti-cancer compound in substantially equivalent ways as the specimen from which they came. This is especially true when a reference (such as Gal) fails to expressly disclose the limitation, fails to provide any technical basis for finding the negative proposition inherent, and otherwise fails to contain any suggestion or motivation for finding the negative proposition. Applicant respectfully submits that the claim amendments, distinguishing evidence and contentions set forth hereinabove satisfy Applicant's *prima facie* burden of establishing patentability. Moreover, for the reasons stated above, Gal does not anticipate the invention claimed herein.

Applicant respectfully submits that the amendments and contentions set forth hereinabove fully distinguish the present invention from all of the prior art cited in the Office Action.

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IV. CONCLUSION

Applicant believes that all rejections have been satisfied, so that all remaining claims of this Application are in condition for allowance as a utility patent.

Respectfully submitted by:

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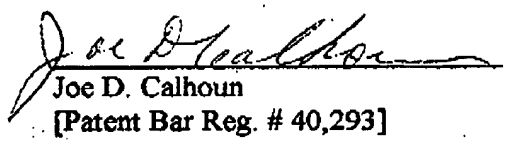

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cc: Charleata A. Carter Ph.D.